

PATENT COOPERATION TREATY


PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

REC'D 07 NOV 2005

Applicant's or agent's file reference 64.WO1	FOR FURTHER ACTION		WIPO See Form PCT/PEA/416 PCT
International application No. PCT/US2004/019279	International filing date (day/month/year) 16.06.2004	Priority date (day/month/year) 17.06.2003	
International Patent Classification (IPC) or national classification and IPC C07D223/00			
Applicant ARENA PHARMACEUTICALS, INC.			
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 7 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input type="checkbox"/> sent to the applicant and to the International Bureau a total of sheets, as follows:</p> <p><input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>			
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the opinion</p> <p><input checked="" type="checkbox"/> Box No. II Priority</p> <p><input checked="" type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input checked="" type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input type="checkbox"/> Box No. VIII Certain observations on the international application</p>			
Date of submission of the demand 15.04.2005		Date of completion of this report 04.11.2005	
Name and mailing address of the International preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized Officer Stix-Malaun, E Telephone No. +49 89 2399-8057	



**INTERNATIONAL PRELIMINARY REPORT
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International application No.
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Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
- ☐ international search (under Rules 12.3 and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4)
 - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

Description, Pages

1-60 as originally filed

Claims, Numbers

1-651 as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/figs
- ☐ the sequence listing (*specify*):
- ☐ any table(s) related to sequence listing (*specify*):

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/figs
- ☐ the sequence listing (*specify*):
- ☐ any table(s) related to sequence listing (*specify*):

* If item 4 applies, some or all of these sheets may be marked "superseded."

**INTERNATIONAL PRELIMINARY REPORT
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Box No. II Priority

1. ☒ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
☒ copy of the earlier application whose priority has been claimed (Rule 66.7(a)).
☐ translation of the earlier application whose priority has been claimed (Rule 66.7(b)).
2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rule 64.1). Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:
- ☐ the entire international application,
- ☒ claims Nos. 139-313, 314(part)-340(part),341-651
because:
- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the said claims Nos. 139-313,314(part)-340(part), 341-651
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
- | | |
|----------------------------|------------------------------------------------------------|
| the written form | <input type="checkbox"/> has not been furnished |
| | <input type="checkbox"/> does not comply with the standard |
| the computer readable form | <input type="checkbox"/> has not been furnished |
| | <input type="checkbox"/> does not comply with the standard |
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
- ☐ See separate sheet for further details

**INTERNATIONAL PRELIMINARY REPORT
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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1,28,65,100
	No: Claims	314(part)
Inventive step (IS)	Yes: Claims	
	No: Claims	1,28,65,100,314(part)
Industrial applicability (IA)	Yes: Claims	1,28,65,100,314(part)
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

III NON-ESTABLISHMENT

The search has only been carried out for the "first group of inventions": claims 1-138,314(part)-340 (part). The applicant has not paid additional fees for one (or more) not yet searched groups of inventions.

No search has been carried out for claims 139-313, 314(part)-340(part),341-651. Accordingly no examination will be carried out with respect to these claims (Rule 66.1e).

The amendments cannot be taken into consideration. They do not form part of the searched invention. Thus, the examination is carried out only on the "first group of inventions" as originally filed.

V REASONED STATEMENT

1. PRIOR ART

The documents cited in the International Search Report

- D1: CH 500 194 A (CIBA-GEIGY AG) 15 December 1970 (1970-12-15)
D2: ORITO ET AL: "TOTAL SYNTHESIS OF PROTOPINE ALKALOIDS"
HETEROCYCLES, vol. 14, no. 1, 1980, pages 11-13, XP001205081
- D4: CHANG, WEI K. ET AL: "Dopamine receptor binding properties of some 2,3,4,5-tetrahydro-1H-3- benzazepin-7-ols with nonaromatic substituents in the 5-position" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS , 2(5), 399-402 CODEN: BMCLE8; ISSN: 0960-894X, 1992, XP002306864
- D5: LADD D L ET AL: "SYNTHESIS AND DOPAMINERGIC BINDING OF 2-ARYLDOPAMINE ANALOGUES: PHENETHYLAMINES, 3-BENZAZEPINES, AND 9-(AMINOMETHYL)FLUORENES" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 29, no. 10, October 1986 (1986-10), pages 1904-1912, XP002031848 ISSN: 0022-2623
- D6: EP-A1-0 285 919 (SCHERING CORP., USA) 12 October 1988 (1988-10-12)
- D7: PAUVERT M ET AL: "Silver nitrate-promoted ring enlargement of 1-

- tribromomethyl-1,2-dihydro- and 1-tribromomethyl-1,2,3,4-tetrahydro-isoquinoline derivatives: application to the synthesis of the anti-anginal zatebradine" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 44, no. 22, 26 May 2003 (2003-05-26), pages 4203-4206, XP004423070 ISSN: 0040-4039
- D8: DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; ORITO, KAZUHIKO ET AL: "Synthetic studies of heterocyclic compounds. I. Alkylation and acylation of 1,2,4,5-tetrahydro-3-methyl-3H-3-benzazepin-2-one" XP002321044 retrieved from STN Database accession no. 1980:407990
- D9: ORITO KAZUHIKO ET AL: "Benzolactams. I. Alkylation of 1,2,4,5-tetrahydro-3-methyl-3H-3-benzazepin-2-one with sodium hydride and alkyl halide" TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 36, no. 8, 1980, pages 1017-1021, XP002171212 ISSN: 0040-4020
- D10: DE 19 44 121 A1 (LABORATOIRE HOUDE) 19 March 1970 (1970-03-19)
- D11: FUCHS ET AL: "TOTAL SYNTHESIS OF (+)-LENNOXAMINE AND (+)-APHANORPHINE BY INTRAMOLECULAR ELECTROPHILIC AROMATIC SUBSTITUTION REACTIONS OF 2-AMIDOACROLEINS" ORG.LETT., vol. 3, no. 24, 2001, pages 3923-3925, XP002321043

have been considered for the examination procedure.

2. NOVELTY

The subject-matter of Claim 314 (formula (II)) is anticipated by D7-D11 (see for passages in the ISR).

The process of claim 1 differs from the one of D4 in the lack of substitution of the nitrogen, from D5 in the presence of the substituent R₂; The process of D6 forms an overlapping part with the presently claimed one (see claims and p. 8 of D6). Due to the present obligatory substituent R₂ bound to a C-H unit it might be seen as a novel selection. The process of claim 28 differs from D1 in the oxo-Substitution, from D2 and D5 in the presence of R₂. It differs from D6 at least in the starting material.

Accordingly claims 1, 28 and the combinations thereof (claims 65 and 100) are

novel(Article 33(2) PCT).

3. INVENTIVE STEP

The subject-matter of Claim does not fulfil the requirements of Article 33(3) PCT for the following reasons:

The closest state of the art for the present application is represented by D6. D6 discloses in a general manner the claimed processes and the combination thereof. As already stated above claim 1 only appears to be a novel selection thereof.

Such a selection can only regarded as being inventive , if the present application exhibits unexpected effects or properties in relation to the rest of the range of D6. However, no such effects or properties are indicated in the application. In the absence of comparative test results or other appropriate information it is not possible to decide whether such a problem has been solved or not.

It should be noted additionally that also D1,D2,D4,D5 disclose analog process steps which have to be seen as technical equivalents due to minor differences such as additional methyl substitution (see explanations above, e.g. D4).

Accordingly inventive step cannot be acknowledged.

VI CERTAIN DOCUMENTS CITED

D3: WO 03/086306 A2 (ARENA PHARMACEUTICALS, INC., USA) 23 October 2003 (2003-10-23)

D3 might become important in the regional phase